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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	**Application No.** 10/685,567	**Applicant(s)** SEN ET AL.	
	Examiner ABIGAIL FISHER	**Art Unit** 1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2009*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5-8* is/are pending in the application.
  4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1 and 5-8* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on *11 May 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.
  Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
  Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  a)☐ All b)☐ Some * c)☐ None of:
    1.☐ Certified copies of the priority documents have been received.
    2.☐ Certified copies of the priority documents have been received in Application No. _____.
    3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
  * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
  Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
  Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 13 2009 has been entered.

Receipt of Amendments/Remarks filed on November 13 2009 is acknowledged. Claims 2-4 and 9-22 were/stand cancelled. Claims 1, 5 and 8 were amended. Claims 1 and 5-8 are pending.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
  (1) Field of the Invention.
  (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A “Sequence Listing” is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required “Sequence Listing” is not submitted as an electronic document on compact disc).

Content of Specification

(a) Title of the Invention: See 37 CFR 1.72(a) and MPEP § 606. The title of the invention should be placed at the top of the first page of the specification unless the title is provided in an application data sheet. The title of the invention should be brief but technically accurate and descriptive, preferably from two to seven words may not contain more than 500 characters.

(b) Cross-References to Related Applications: See 37 CFR 1.78 and MPEP § 201.11.

(c) Statement Regarding Federally Sponsored Research and Development: See MPEP § 310.

(d) The Names Of The Parties To A Joint Research Agreement: See 37 CFR 1.71(g).

(e) Incorporation-By-Reference Of Material Submitted On a Compact Disc: The specification is required to include an incorporation-by-reference of electronic documents that are to become part of the permanent United

States Patent and Trademark Office records in the file of a patent application. See 37 CFR 1.52(e) and MPEP § 608.05. Computer program listings (37 CFR 1.96(c)), “Sequence Listings” (37 CFR 1.821(c)), and tables having more than 50 pages of text were permitted as electronic documents on compact discs beginning on September 8, 2000.

(f) Background of the Invention: See MPEP § 608.01(c). The specification should set forth the Background of the Invention in two parts:

  (1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."

  (2) Description of the Related Art including information disclosed under 37 CFR 1.97 and 37 CFR 1.98: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."

(g) Brief Summary of the Invention: See MPEP § 608.01(d). A brief summary or general statement of the invention as set forth in 37 CFR 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

(h) Brief Description of the Several Views of the Drawing(s): See MPEP § 608.01(f). A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.

(i) Detailed Description of the Invention: See MPEP § 608.01(g). A description of the preferred embodiment(s) of the invention as required in 37 CFR 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.

(j) Claim or Claims: See 37 CFR 1.75 and MPEP § 608.01(m). The claim or claims must commence on separate sheet or electronic page (37 CFR 1.52(b)(3)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps. See 37 CFR 1.75 and MPEP § 608.01(i)-(p).

(k) Abstract of the Disclosure: See MPEP § 608.01(f). A brief narrative of the disclosure as a whole in a single paragraph of 150 words or less commencing on a separate sheet following the claims. In an international application which has entered the national stage (37 CFR 1.491(b)), the applicant need not submit an abstract commencing on a separate sheet if an abstract was published with the international application under PCT Article 21. The abstract that appears on the cover page of the pamphlet published by the International Bureau (IB) of the World Intellectual Property Organization (WIPO) is the abstract that will be used by the USPTO. See MPEP § 1893.03(e).

(l) Sequence Listing. See 37 CFR 1.821-1.825 and MPEP §§ 2421-2431. The requirement for a sequence listing applies to all sequences disclosed in a given application, whether the sequences are claimed or not. See MPEP § 2421.02.

The disclosure is objected to because of the following informalities: the specification does not possess a detailed description of the drawings.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takada et al. (US Patent No. 6117455, cited in the Office action mailed on 1/8/08) in view of Jabes et al. (Antimicrobial Agents and Chemotherapy, 1994).

Applicant Claims

Applicant claims a biodegradable inhalable microparticle composition consisting of anti-tubercular drugs Rifabutin and Isoniazid and a biodegradable polymer for drug delivery wherein the ratio of drugs to polymer is from about 1:2 to 2:1 and wherein the two anti-tubercular drugs are used in the ratio of about 1:2 to 2:1.

Determination of the Scope and Content of the Prior Art
(MPEP §2141.01)

Takada et al. is directed to microcapsules, which includes microparticles containing amorphous water-soluble physiologically active substance and a polymer (column 1, lines 6-9). Takada et al. teach the amount of the active is from 0.001 to 90% (W/W) (column 7, lines 48-49). The active agent can be an anti-tuberculosis agent such as isoniazid or ethanbutol (column 7, lines 13-14). The average particle size is from 1 nm to 10 um for the active substance (column 7, lines 54-55). The average diameter of the microcapsules range from about 0.5 to about 400 μm with 2 to about 200 μm being preferable (column 12, lines 63-65). One particular polymer listed as being suitable is polylactic acid (column 7 line 60). It is taught that the amount of polymer ranges from about 0.5 to about 90% (column 9, lines 44-46). The amount of polymer utilized depends upon the degree of pharmacological activity, release rate and release period of the active substance (column 9, lines 37-39).

Ascertainment of the Difference Between Scope the Prior Art and the Claims
(MPEP §2141.012)

Takada et al. does not disclose a specific drug to polymer ratio or a drug to drug ratio. Takada et al. does not specify utilizing Rifabutin and Isoniazid. However, this deficiency is cured by Jabes et al.

Jabes et al. is directed to the effectiveness of Rifabutin alone or in combination with Isoniazid in preventive therapy of mouse tuberculosis. Jabes et al. found that rifabutin alone or in combination with isoniazid proved to be a valid candidate for tuberculosis preventative therapy (abstract). The ratio of rifabutin to isoniazid is 1:2.5 (table 1).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art to combine the teachings of Takada et al. and Jabes et al. and utilize two anti-tubercular drugs such as isoniazid and rifabutin. One of ordinary skill in the art would have been motivated to utilize both isoniazid and rifabutin as Jabes et al. teach it is a specific combination of anti-tuberculosis drugs which are known to be effective in tuberculosis therapy.

Regarding the claimed ratio of drug to polymer, it would have been obvious to one of ordinary skill in the art to optimize the ratio of drug to polymer depending on the desired release rate and period desired as taught by Takada et al. The amount of the polymer in the composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

Regarding the claimed ratio of drug to drug, it would have been obvious to one of ordinary skill in the art to determine the optimal ratio of the two anti-TB drugs. One of ordinary skill in the art would have been motivated to start with a 1:2.5 ratio of the two drugs as this is the ratio taught by Jabes et al. and then optimize the ratio from that point. A 1:2.5 ratio of the drugs reads on the instant claimed ratio. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. **In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).**

Regarding the claimed particle size, Takada et al. teach an amount that overlaps that instantly claimed. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. **See MPEP 2144.05 [R-5]**

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants argue that the instant application is directed to a microparticle that contains both the drug and the polymer where as Takeda teaches microcapsule containing both the drug and polymer. It is argued that although Takada states the term microcapsule includes microcapsules and microparticles, Takada teaches that the active substance is in the form of microcapsules ranging from 1 nm to 10 µm whereas in the formation of microcapsules the diameter is 0.5 µm to 400 µm. Therefore, there is a difference between the microcapsules and microparticle. The instant claims require that both the drug and the polymer are microparticles.

Applicants' arguments filed November 13 2009 have been fully considered but they are not persuasive.

While the examiner acknowledges that Takeda teaches that there may be some particle size difference between microparticles and microcapsules. Takeda teaches a particle size for the microcapsules that overlap that instantly claimed. Therefore a *prima facie* case of obviousness exists. The particle size of the microcapsules is still microparticulate.

Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

Claims 1 and 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barrow et al. (US Patent No. 6264991, cited in the Office action mailed on 8/5/09) in view of Jabes et al.

Applicant Claims

Applicant claims a biodegradable inhalable microparticle composition consisting of anti-tubercular drugs Rifabutin and Isoniazid and a biodegradable polymer for drug delivery wherein the ratio of drugs to polymer is from about 1:2 to 2:1 and wherein the two anti-tubercular drugs are used in the ratio of about 1:2 to 2:1.

Determination of the Scope and Content of the Prior Art
(MPEP §2141.01)

Barrow et al. is directed to compositions for treating intracellular infections (title). The compositions are microspheres that have diameter from about 1 to about 10 microns (column 4, lines 34-35). It is taught that in most known treatment regimens, TB is treated with two or more drugs (column 5, lines 46-47). The invention of Barrow et al. can be utilized to administer a combination of one or more microencapsualted drugs (column 5, lines 49-51). It is taught that the invention is well adapted to treating TB and any drug capable of treating TB can be administered by the method of the invention such drugs include rifampicin and rifabutin (column 5, lines 38-40). Table A is directed to the dosage recommendations for various ant-TB drugs in adults and children which include isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin. A daily dose for adults of isoniazid is 5 mg/kg and Rifampin is 10 mg/kg. The particles can be delivered intravenously, orally, via inhalation, etc. (column 6, lines 32-36). Polymers that can be utilized to form the microspheres include poly(lactide) (claim 13).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Barrow et al. do not specify a ratio of drug to polymer or drug to drug. Barrow et al. does not exemplify a formulation comprising more than one drug capable of treating TB or that a combination of isoniazid and rifabutin can be administered. However, this deficiency is cured by Jabes et al.

Jabes et al. is directed to the effectiveness of Rifabutin alone or in combination with Isoniazid in preventive therapy of mouse tuberculosis. Jabes et al. found that rifabutin alone or in combination with isoniazid proved to be a valid candidate for tuberculosis preventative therapy (abstract). The ratio of rifabutin to isoniazid is 1:2.5 (table 1).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art to combine the teachings of Barrow et al. and Jabes et al. and utilize two anti-tubercular drugs such as isoniazid and rifabutin. One of ordinary skill in the art would have been motivated to utilize both isoniazid and rifabutin as Jabes et al. teach it is a specific combination of anti-tuberculosis drugs which are known to be effective in reducing the mycobacterial load. One of ordinary skill in the art would have additionally been motivated to formulate this type of composition because Barrow et al. teach that their invention can incorporate any drug known to treat TB and that most known treatment regimens utilize two or more drugs to treat TB.

Regarding the claimed ratio of drug to polymer, Barrow et al. does not specify the ratio of polymer to drug. Barrow et al. only exemplifies formulations with one percentage of drug, however it would have been obvious to one of ordinary skill in the art to vary the drug to polymer ratio to determine the optimal release rate of the drug. The amount of the polymer in the composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. **In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).**

Regarding the claimed drug to drug ratio, Barrow et al. teach that the daily dose for adults of isoniazid is 5 mg/kg and Rifampin is 10 mg/kg. This corresponds to a 1:2 ratio for these particular drugs. One of ordinary skill in the art would have been motivated to utilize a 1:2.5 ratio of isoniazid and Rifabutin as this is the ratio taught by

Jabes et al. It would have been obvious to one of ordinary skill in the art to optimize the ratio of isoniazid to a second drug in order to determine the optimal ratio. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. **In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).**

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants argue that the use of the transitional language consisting language excludes the use of additional active agents to be used in combination with Rifabutin and Isoniazid. It is argued that Barrow teaches utilizing a combination of drugs in the treatment of tuberculosis. One option is the use of a three drug combo for 8 weeks followed by 16 weeks of a two drug combo (isoniazid and rifampin). In all of the options it is recommended that ethambutol or streptomycin is added if the resistance to isoniazid is more than 4%.

Applicants' arguments filed November 13 2009 have been fully considered but they are not persuasive.

Firstly, the examiner notes that the instant claims are directed to a composition. Therefore, the transitional claim language applies only to the composition. The instant claims do not exclude a second formulation that is added in conjunction or in the weeks following/preceding administration of a rifabutin/isoniazid combination. Therefore, while the options of Barrow teach that a four drug combo can be administered first for several weeks followed by administration of a two drug combo, the administration of the four drug combo is not excluded as long as the additional drugs are not present in the composition consisting of rifabutin and isoniazid. Barrow teaches a drug combo as pointed out by applicants of isoniazid and rifampin. Rifabutin and rifampin are both drugs of the rifamycin group. Jabes et al. teach that the combination of isoniazid and rifabutin is a known drug combo, therefore, their combination is obvious. Since Barrow teaches that most known drug treatments of tuberculosis utilize two or more drugs, one of ordinary skill in the art would have been motivated to utilize a specific known combination which is isoniazid and rifabutin.

Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

Claims 1 and 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quenelle et al. (Antimicrobial Agents and Chemotherapy, 2001) in view of

Jabes et al. and Sharma et al. (Pharmaceutical Research, 2001, cited on PTO Form 1449).

Applicant Claims

Applicant claims a biodegradable inhalable microparticle composition consisting of anti-tubercular drugs Rifabutin and Isoniazid and a biodegradable polymer for drug delivery wherein the ratio of drugs to polymer is from about 1:2 to 2:1 and wherein the two anti-tubercular drugs are used in the ratio of about 1:2 to 2:1.

Determination of the Scope and Content of the Prior Art
(MPEP §2141.01)

Quenelle et al. is directed to the treatment of tuberculosis using a combination of sustained release rifampin microspheres and oral dosing with isoniazid. The formulations comprise small microspheres 1 to 10 microns or large microspheres 10 to 150 microns (page 1637, last paragraph). Quenelle et al. teach that in previous publications it was taught that liposomes can be used to deliver biological agents. It is taught that the poly(lactide-co-glycolide) microspheres allow greater flexibility with respect to the timed release of encapsulated material and are more stable than liposomes. It is taught that while biological degradation of poly(lactide-co-glycolide) microspheres is well understood, biological degradation of liposomes is not. Additionally, microspheres can be formulated to hold a larger amount of drug for longer sustained release than liposomes (page 1643, last paragraph).

Ascertainment of the Difference Between Scope the Prior Art and the Claims
(MPEP §2141.012)

Quenelle et al. et al. do not teach utilizing poly-lactic acid as the biodegradable polymer. Quenelle et al. does not teach utilizing a combination of isoniazid and rifabutin. However, these deficiencies are cured by Jabes et al. and Sharma et al.

Jabes et al. is directed to the effectiveness of Rifabutin alone or in combination with Isoniazid in preventive therapy of mouse tuberculosis. Jabes et al. found that rifabutin alone or in combination with isoniazid proved to be a valid candidate for tuberculosis preventative therapy (abstract). The ratio of rifabutin to isoniazid is 1:2.5 (table 1). It is taught that Rifabutin is an intrinsically more potent antimycobacterial agent than rifampin because of its higher intracellular levels, its higher levels in tissue and its superior bactericidal activity (page 2346, second paragraph).

Sharma et al. is directed to inhalable microparticles containing drug combinations to target alveolar macrophages for the treatment of pulmonary tuberculosis (title). It is taught that single-drug therapy of tuberculosis (TB) is disfavored for fear of drug resistance (page 1402, right column, third paragraph). Therefore the inhalable microparticles contain two anti-TB drugs H (isoniazid) and R (rifampicin). The formulation is disclosed as containing one part of drug to three parts of PLA (poly lactic acid) (page 1406, formulation). The size ranges of the formulation were from 0.5 to 3 microns (table 1). The ratio of isoniazid to rifampicin is from 3:2 to 1:1 (table 1). It is taught that the microparticle incorporated R and H could establish higher drug concentrations in macrophages as compared to equivalent amounts of drugs in solution, thus confirming the argument that a larger amount of drug was delivered to the cells (page 1407, results and discussions, paragraph 4). It is taught that the microparticles release about 20 to 30% of their content within 15 minutes and the remaining amount is released slowly over 4 weeks.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Jabes et al., Quenelle et al. and Sharma et al. and utilize a combination of rifabutin and isoniazid. One of ordinary skill in the art would have been motivated to utilize this combination as Rifabutin is taught by Jabes et al. as being more potent that rifampin and that the combination of rifabutin and isoniazid is proven to be a valid candidate for tuberculosis preventative therapy.

Regarding the claimed ratio of drug to drug, it would have been obvious to one of ordinary skill in the art to determine the optimal ratio of the two anti-TB drugs. One of ordinary skill in the art would have been motivated to start with a 1:2.5 ratio of the two drugs as this is the ratio taught by Jabes et al. and then optimize the ratio from that point. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art to determine the optimal ratio isoniazid and rifampicin in order to treat tuberculosis. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

Regarding the claimed ratio of drug to polymer, Quenelle et al. do not specify the ratio of polymer to drug. Sharma et al. teach a drug to polymer ratio of 1:3. It would have been obvious to one of ordinary skill in the art to vary the drug to polymer ratio to determine the optimal release rate of the drug. The amount of the polymer in the composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. **In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).**

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Examiner
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AF

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